NO:54), which had previously been shown to cause splenomegaly and hypergammaglobulinemia upon *in vivo* administration in mice, and studied the pattern and kinetics of cytokine production at both the splenic mRNA and serum protein levels. Zhao et al. (1997) Antisense Nucleic Acid Drug Dev 7:495-502. Following i.p. administration of 50 mg/kg of oligonucleotide, significant increases in the splenic mRNA levels of IL-6, IL-12 p40, IL-1β, and IL-1Ra and serum levels of IL-6, IL-12, MIP-1β, and MCP-1 were observed. In contrast, no significant differences in splenic mRNA levels of IL-2, IL- 4, IL-5, IL-9, IL-13, IL-15, IFN-γ, or MIF or serum levels of IL-2, IL-4, IL-5, IL-10, IFN-γ, or GM-CSF were detected. These studies show a distinct pattern and kinetics of cytokine production following oligonucleotide administration and further demonstrate that cytokine induction is not a general property of phosphorothioate oligonucleotides but is dependent on the sequence and dose of the oligonucleotides. Serum release of IL-1, IL-6, IL-12 and TNF-α was also confirmed by Lipford et al. Lipford, GB et al. (1997) Eur J Immunol 27:2340-2344.

(2) On pages 12-13, replace the paragraph beginning at line 30 on page 12 with the following:

In another embodiment the CpG oligonucleotide has a sequence including at least the following formula:

5' $TCNTX_1X_2CGX_3X_4$ 3' (SEQ ID NO:89)

wherein X_1, X_2, X_3, and X_4 are nucleotides, and N is a nucleic acid sequence composed of from 0-25 nucleotides.

(3) On page 36, replace the paragraph at lines 18-27 with the following:

In another embodiment the invention provides an isolated CpG oligonucleotide represented by the formula:

5' $N_1X_1X_2CGX_3X_4N_2$ 3'

wherein at least one nucleotide separates consecutive CpGs; X_1X_2 is selected from the group consisting of TpT, CpT, TpC, and ApT; X_3X_4 is selected from the group consisting of GpT,

GpA, ApA and ApT; N is any nucleotide and N_1 and N_2 are nucleic acid sequences composed of from about 0-25 N's. In a preferred embodiment N_1 and N_2 of the nucleic acid do not contain a CCGG quadmer or more than one CCG or CGG trimer. In another preferred embodiment the CpG oligonucleotide has the sequence 5' $TCN_1TX_1X_2CGX_3X_4$ 3' (SEQ ID NO: 89).

(4) On page 39, replace the paragraph beginning at line 7 with the following:

The nucleic acid sequences of the invention which are useful for inducing immune remodeling are those broadly described above. Exemplary sequences include but are not limited to those sequences shown in Table 1-7 as well as TCCATGTCGCTCCTGATGCT (SEQ ID NO:35), TCCATGTCGTTCCTGATGCT (SEQ ID NO:43), TCGTCGTTGTCGTTGTCGTT (SEQ ID NO:79), TCGTCGTTTTGTCGTTTTGTCGTT (SEQ ID NO:80), TCGTCGTTGTCGTTTTGTCGTT (SEQ ID NO:81), GCGTGCGTTGTCGTTGTCGTT (SEQ ID NO:82), TGTCGTTTGTCGTTTGTCGTT (SEQ ID NO:84), TGTCGTTGTCGTTGTCGTT (SEQ ID NO:86), TCGTCGTCGTCGTT (SEQ ID NO:87), TCCTGTCGTTCCTTGTCGTT (SEQ ID NO:68), TCCTGTCGTTTTTTGTCGTT (SEQ ID NO:70), TCGTCGCTGTCTGCCCTTCTT (SEQ ID NO:72), TCGTCGCTGTTGTCGTTTCTT (SEQ ID NO:73), TCCATGACGTTCCTGACGTT (SEQ ID NO:71), GTCG(T/C)T and TGTCG(T/C)T.

(5) On Page 51, replace the paragraph beginning at line 16 with the following:

Microbial stimuli and synthetic oligonucleotides. Phosphorothioate-stabilized oligonucleotides (ODN) were synthesized by TibMolBiol (Berlin, Germany). ODN sequences 'CG1' (= ODN 1668, containing a 'CG-motif' marked with bold letters: 5'-TCC-AT**G-ACG-TT**C-CTG-ATG-CT; SEQ ID NO:24) and control GC-ODN ('inverted CG' = ODN 1720: 5'-TCC-AT**G-AGC-TT**C-CTG-ATG-CT; SEQ ID NO:29) were taken from Krieg, AM et al. (1995) Nature 374:546-549. A second CpG-ODN 'CG2' (= ODN IL12p40: 5'-AGC-TAT-**GAC-GTT**-CCA-AGG; SEQ ID NO:30) and control ODN 'nCG' ('non-CG' = ODN AP1, without CG-motif: 5'-GCT-TGA-TGA-CTC-AGC-CGG-AA; SEQ ID NO:65) were described recently. Lipford, GB et al. (1997) Eur J Immunol 27:2340-2344. LPS from *E. coli* was purchased from Sigma (Munich, Germany). *Listeria monocytogenes* came from ATCC

(American type culture collection strain 43251) and were grown in brain hear infusion (Difco, Detroit, USA) in overnight cultures. Number of bacteria was determined by OD_{600} and checked by plating 10 µl aliquots of a serial 10-fold dilution on Columbia blood agar plates and counting the colony forming units after overnight incubation at 37°C.

(6) On page 65, replace Table 1 with the following:

Table 1

ODN	Sequence (5' → 3')	SEQ ID NO:
1	GCTAGACGTTAGCGT	1
1a	·····T······	2
1b	·····Z······	3
1c	··········Z··	4
1d	··AT·····GAGC·	5
2	ATGGAAGGTCCAGCGTTCTC	6
2a	··C··CTC··G·····	7
2b	··Z··CTC·ZG··Z·····	8
2c	··Z··CTC··G·····	9
2d	··C··CTC··G·····Z··	10
2e	··········A·····	11
3D	GAGAACGCTGGACCTTCCAT	12
3Da	·····C·····	13
3Db	·····C·····G··	14
3Dc	···C·A··········	15
3Dd	·····Z··········	16
3De	··········Z·····	17
3Df	·····A··········	18
3Dg	·····CC·G·ACTG··	19
3M	TCCATGTCGGTCCTGATGCT	20
3Ma	·····CT··········	21
3Mb	·····Z··········	22
3Mc	··········Z·····	23
3Md	·····A··T·····	24
3Me	··········C··A·	25

4	TCAACGTT
4a	····GC··
4b	···GCGC·
4c	···TCGA·
4d	··TT··AA
4e	-·····-·
4f	C·····-·
4g	--·····CT
4h	·····-·C

D 4 cont'd

(7) On page 66, replace Table 2 with the following:

Table 2

5a	ATGGACTCTCCAGCGTTCTC	(SEQ ID NO:26)
5b	·····AGG····A·····	(SEQ ID NO:11)
5c	··C·····G·····	(SEQ ID NO:7)
5d	····AGG··C··T·····	(SEQ ID NO:27)
5e	··C·····G··Z·····	(SEQ ID NO:28)
5f	··Z·····ZG··Z·····	(SEQ ID NO:8)
5g	··C·····G·····Z··	(SEQ ID NO:10)
	GCATGACGTTGAGCT	(SEQ ID NO:5)
	GCTAGATGTTAGCGT	(SEQ ID NO:2)

D 7

(8) On page 67, replace Table 3 with the following:

Table 3

512 SEQ ID NO:20	TCCATGTCGGTCCTGATGCT
1637 SEQ ID NO:31	·····C·····
1615 SEQ ID NO:32	·····G·····
1614 SEQ ID NO:33	·····A·····
1636 SEQ ID NO:34	·····A·····
1634 SEQ ID NO:35	·····C·····

D 8

1619 SEQ ID NO:43	·····T·····
1618 SEQ ID NO:24	·····A··T·····
1639 SEQ ID NO:36	·····AA··T·····
1707 SEQ ID NO:37	·····A··TC·····
1708 SEQ ID NO:38	·····CA··TG·····

D8 cont'd

(9) On page 68, replace Table 4 with the following:

Table 4

D9

1585	ggGGTCAACGTTGACgggg	(SEQ ID NO:39)
1629	·····gtc·····	(SEQ ID NO:40)
1613	GCTAGACGTTAGTGT	(SEQ ID NO:41)
1769	·····Z·····	(SEQ ID NO:42)
1619	TCCATGTCGTTCCTGATGCT	(SEQ ID NO:43)
1765	·····Z·····	(SEQ ID NO:44)

(10) On page 69, replace Table 5 with the following:

Table 5

D10

ODN	Sequence (5' → 3')	SEQ ID NO:
1751	ACCATGGACGATCTGTTTCCCCTC	45
1758	TCTCCCAGCGTGCGCCAT	46
1761	TACCGCGTGCGACCCTCT	47
1776	ACCATGGACGAACTGTTTCCCCTC	48
1777	ACCATGGACGAGCTGTTTCCCCTC	49
1778	ACCATGGACGACCTGTTTCCCCTC	50
1779	ACCATGGACGTACTGTTTCCCCTC	51
1780	ACCATGGACGGTCTGTTTCCCCTC	52
1781	ACCATGGACGTTCTGTTTCCCCTC	53
1823	GCATGACGTTGAGCT	5
1824	CACGTTGAGGGGCAT	55
1825	CTGCTGAGACTGGAG	56
1828	TCAGCGTGCGCC	57
1829	ATGACGTTCCTGACGTT	58

1830	RANDOM SEQUENCE	
1834	TCTCCCAGCGGGCGCAT	59
1836	TCTCCCAGCGCGCGCCAT	60
1840	TCCATGTCGTTCCTGTCGTT	61
1841	TCCATAGCGTTCCTAGCGTT	62
1842	TCGTCGCTGTCTCCGCTTCTT	63
1851	TCCTGACGTTCCTGACGTT	64

D10 cont'd

(11) On page 70, replace Table 6 with the following:

Table 6

ODN	Sequence (5' → 3')	SEQ ID NO:
1840	TCCATGTCGTTCCTGTCGTT	61
1960	TCCTGTCGTTCCTGTCGTT	66
1961	TCCATGTCGTTTTTGTCGTT	67
1962	TCCTGTCGTTCCTTGTCGTT	68
1963	TCCTTGTCGTTCCTGTCGTT	69
1965	TCCTGTCGTTTTTTGTCGTT	70
1966	TCGTCGCTGTCTCCGCTTCTT	63
1967	TCGTCGCTGTCTGCCCTTCTT	72
1968	TCGTCGCTGTTGTCGTTTCTT	73
1979	TCCATGTZGTTCCTGTZGTT	74
1982	TCCAGGACTTCTCTCAGGTT	75
1990	TCCATGCGTGCGTGCGTTTT	76
1991	TCCATGCGTTGCGTTGCGTT	77
2002	TCCACGACGTTTTCGACGTT	78
2005	TCGTCGTTGTCGTTGTCGTT	79
2006	TCGTCGTTTTGTCGTTTTGTCGTT	80
2007	TCGTCGTTGTCGTTTTGTCGTT	81
2008	GCGTGCGTTGTCGTTGTCGTT	82
2010	GCGGCGGGCGGCGCGCGCCC	83
2012	TGTCGTTTGTCGTTTGTCGTT	84
2013	TGTCGTTGTCGTTGTCGTTGTCGTT	85
2014	TGTCGTTGTCGTTGTCGTT	86
2015	TCGTCGTCGTCGTT	87
2016	TGTCGTTGTCGTT	88
1841	TCCATAGCGTTCCTAGCGTT	62

D11

(12) On page 71, replace Table 7 with the following:

D12

Table 7

ODN	Sequence (5' → 3')	SEQ ID NO:
1962	TCCTGTCGTTCCTTGTCGTT	68
1965	TCCTGTCGTTTTTTGTCGTT	70
1967	TCGTCGCTGTCTGCCCTTCTT	72
1968	TCGTCGCTGTTGTCGTTTCTT	73
2005	TCGTCGTTGTCGTTGTCGTT	79
2006	TCGTCGTTTTGTCGTTTTGTCGTT	80
2014	TGTCGTTGTCGTTGTCGTT	86
2015	TCGTCGTCGTCGTT	87
2016	TGTCGTTGTCGTT	88
1668	TCCATGACGTTCCTGATGCT	24
1758	TCTCCCAGCGTGCGCCAT	46

D12 cont'd

(13) On page 56, replace the paragraph beginning at line 4 as follows:

The induction of splenic hematopoiesis was CpG-ODN dose and sequence dependent (Fig. 4, also see Fig. 3D, table 1b and 1c). Sequences lacking the 'CpG-motif' (nCG) failed to induce extramedullary hematopoiesis and CG inversion (GC-ODN) almost completely abolished the hematopoietic effect of the ODN CG1. Single shot injection of CpG ODN also compared well with the documented hematopoietic activity triggered by LPS (Fig. 4). Apte, RN et al. (1976) J Cell Physiol 71-78; Apte, RN et al. (1976) Exp Hematol 4:10-18; Staber, FG et al. (1980) Proc Natl Acad Sci USA 77:4322-4325. In addition to the granulocyte-macrophage progenitors, the number of pure erythroid progenitors post CpG ODN injection was also increased as determined by the number of Burst-forming Units (BFU-E) per spleen (Fig. 5). Analysis of peripheral blood over 12 days revealed no significant changes apart from a transient leukocytosis at day 2-4. Thus the transient splenomegaly observed in ssDNA injected mice was CpG motif dependent and associated with extramedullary hematopoiesis.

D13

(14) On page 57, replace the paragraph beginning at line 14 as follows:

CpG-ODN mediate radioprotective effects in myelosuppression. Hematopoietic progenitor cells are considered as rather radioresistant. Morrison, SJ et al. (1995) Annu Rev Cell Dev Biol 11:35-71. Since CpG-ODN induce extramedullary hematopoiesis via mobilization of

D14

CFU-S to the spleen we analyzed whether CpG-ODN could mediate radioprotective effects in sublethally irradiated mice. CpG challenge of sublethally irradiated mice (4 Gy) lead within 14 days to a 4 fold increase of splenic GM-CFU (Fig. 7A). Next, we addressed the question whether CpG-ODN driven hematopoiesis in sublethally irradiated mice allows accelerated recovery of the immune system. Two experimental systems were chosen: one, the induction of CTL responses to proteinaceous antigens (Lipford, GB et al. (1997) Eur J Immunol 27:2340-2344), and two, resistance to the intracellular pathogen *Listeria monocytogenes* (Endres, R et al. (1997) Immunity 7:419-432). Mice were treated with CpG-ODN within 30 minutes after sublethal irradiation (4 Gy), allowed to recover for 18 days and thereafter immunized subcutaneously (s.c.) with ovalbumin (OVA) containing liposomes plus QuilA as adjuvant. After 4 days cells of draining lymph nodes were harvested, cultured for an additional four days and assayed for OVA specific CTL activity. As detailed in Fig. 7B lymphocytes from CpG-ODN treated irradiated mice displayed an enhanced CTL response compared to non-treated irradiated mice. Basically similar results were obtained in an infection model using *L. monocytogenes* infection at day 14. Overall the data given in Fig. 7 demonstrate a correlation between CpG-ODN induced extramedullary hematopoiesis and the ability to mount cytotoxic T cell responses or protective immune responses towards bacterial infections. CpG-ODN compensate radiation induced damage of the lympho-hematopoietic system by accelerating regeneration from hematopoietic progenitor cells.

D 14 cont'd

In the Claims

Please amend claims 11, 40, 49, 62, and 68 by substituting for them the following rewritten claims.

11. (Twice Amended) The method of claim 1, wherein the CpG oligonucleotide has a sequence including at least the following formula:

5' TCNTX$_1$X$_2$CGX$_3$X$_4$ 3' (SEQ ID NO:89)

wherein X_1, X_2, X_3, and X_4 are nucleotides, N is a nucleic acid sequence composed of from about 0-25 nucleotides.

D 15